REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 17 has been amended to require that the functional DNA sequence comprises a selectable marker gene in accordance with last paragraph of the specification on page 8. The remaining claims incorporate this limitation by their direct or indirect dependence on claim 17.

Claim 55 has been amended to correct some typographical errors. Claim 55 remains supported by, for example, point (9) on page 5 of the specification.

A number of claims are amended to restore "Rosa26 locus," in accordance with the Examiner's comments in the first paragraph on page 3.

Applicants do not believe this amendment introduces new matter. An early notice to that effect is earnestly solicited.

Claims 17-19, 24, 25, 28-30, 32-41, 43-46, 48 and 53-58 were rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. In response, Applicants respectfully submit that the claims satisfy the written description requirement.

With respect to claim 17, and the Examiner's concern regarding "Rosa26 gene," Applicants have changed the claims back to "Rosa26 locus" in accordance with the Examiner's comments in the first paragraph on page 3.

With respect to the Examiner's concern regarding "a DNA sequence which can be converted into such gene expression cassette," Applicants point to the third line of point 2 on page 4 of the specification.

With respect to claims 53-55, there is no requirement that what is claimed appear *ipsis verbis* in the specification. It is sufficient that the concept embodied by the language is present in the specification. *See, e.g., In re Anderson,* 176 USPQ 331, 336 (CCPA 1973), for the proposition that in determining whether an amendment to a claim constitutes new matter, the question is not whether the added word is a word that is used in the application as filed, but whether the concept embodied by the added word is present in the original specification.

With respect to claim 56, the first line of the last paragraph on page 9 clearly indicates that the upcoming section relates to "methods (1) to (3) of the invention" and that they relate to "recombinase mediated recombination." The next to last line on page 9 refers to "a recombination vector as defined above." Method (1) on page 4 clearly provides for recombinase mediated recombination "with a recombination vector comprising said functional DNA sequence flanked by a pair of first recombinase recognition sites (RRSs)." Subsection (a2) on page 9 further provides that the donor DNA comprises "the same two mutually incompatible first RRSs contained in the acceptor DNA." Respectfully, the Examiner's failure to find description here is not understood.

In view of the foregoing, Applicants respectfully submit that the claims do not introduce new matter. An early notice to that effect is earnestly solicited.

Claims 32, 33, 43-45, 55 and 56 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, Applicants respectfully submit that the claims are definite.

With respect to claim 32, Applicants take issue that in order for a term to be "definite," it must be defined in the specification. Indefiniteness means not precise, or not capable of exact boundaries. It does not, as the Examiner implies, mean no definition is given. Thus, persons skilled in the art fully understand what is meant by "inducible ubiquitous promoters" and "inducible tissue specific promoters." Moreover, the first paragraph on page 8 of the specification gives examples of ubiquitous and tissue specific promoters. The specification then teaches such promoters can be either constitutive or inducible. The metes and boundaries of the phrases "inducible ubiquitous promoters" and "inducible tissue specific promoters" would be readily understood to persons skilled in the art. If the promoter is ubiquitous and inducible, then it is an "inducible ubiquitous promoter." If the promoter is tissue specific and inducible, then it is an "inducible tissue specific promoter." Applicants discern no ambiguity here.

Respectfully, these are standard, textbook terms. Indeed, the terms "ubiquitous," "cell type-specific," "constitutive," and "inducible" promoter mentioned in claim 32 are defined in chapter 11.2 of the textbook by Torres & Kühn (1997) Laboratory Protocols for Conditional Gene Targeting, Oxford University Press, USA; ISBN-10: 019963677X, ISBN-13: 978-0199636778.

Since the meaning of "inducible ubiquitous promoters" and "inducible tissue specific promoters" is clear to persons skilled in the art, there is no indefiniteness even if there are no specific examples given for either type. The Examiner's concern, to the extent it is based on indefiniteness, is not properly based.

With respect to claim 33, definiteness does not require either definitions or structure in the specification. All that is required is that a person having ordinary skill in the art understands

what is intended. The Examiner states that the abbreviations in claim 33, and the promoters claimed in claim 33 were not known in the art. What is not stated is that the Examiner attempted to find them, but could not. Applicants are filing an information disclosure statement containing a number of references that show the various promoters mentioned in claim 33 were, in fact, known in the art as follows:

CAGGS: Okabe, M., Ikawa, M., Kominami, K., Nakanishi, T. and Nishimune, Y. (1997) FEBS Lett., 407, 313-319.
hCMV: Chung S, Andersson T, Sonntag KC, et al Stem cells 2002; 20: 139-145.
PGK: McBurney MW, Staines WA, Boekelheide K, Parry D, Jardine K, Pickavance L., (1994) Dev Dyn. 200:278-93.
FABP: Saam & Gordon, J. Biol. Chem., 274:38071-38082 (1999)
Lck: Orban et al., Proc. Natl. Acad. Sci. USA, 89:6861-5 (1992)
CamKII: Tsien et al., Cell 87: 1317-1326 (1996)
CD19: Rickert et al., Nucleic Acids Res. 25:1317-1318 (1997)
Keratin: Li et al., Development, 128:675-88 (201)
Albumin: Postic & Magnuson, Genesis, 26:149-150 (2000)
aP2: Barlow et al., Nucleic Acids Res., 25 (1997)
Insulin: Ray et al., Int. J. Pancreatol. 25:157-63 (1999)
MCK: Brüning et al., Molecular Cell 2:559-569 (1998)
MyHC: Agah et al., J. Clin. Invest., 100:169-179 (1997)
WAP: Utomo et al., Nat. Biotechnol. 17:1091-1096 (1999)
Col2A: Ovchinnikov et al., Genesis, 26:145-146 (2000))
Mx: Kühn et al. Scinence, 269:1427-1429 (1995)
Tet: Urlinger et al., Proc. Natl. Acad. Sci. USA, 97:7963-8 (2000)
Trex: Yao F, Eriksson E., Hum Gene Ther. 1999 Feb 10;10(3):419-27.

Respectfully, claim 33 is also definite.

With respect to the Examiner's concern regarding claim 45, once again, inactive positive selection markers were, in fact, known in the art. See, for example, Fukushige S. Sauer B Proc Natl Acad Sci USA 1992 Sept 1; 89(17):7905-9, Genomic targeting with a positive-selection lox integration vector allows highly reproducible gene expression in mammalian cells, which is included in the accompanying information disclosure statement.

Claim 45 is likewise definite.

With respect to claim 55, the Examiner's concern is unjustified. Claim 55 expressly requires that "expression of the gene of interest models a disease state in said animal model." This language excludes any embodiment, including the hypothetical alleged by the Examiner, wherein the expression of the gene of interest is incapable of modeling the disease state in the animal model.

Claim 55 is definite.

Finally, with respect to claim 56, Applicants point out that the term "mutually incompatible RRS" mentioned in claim 56 is defined in Schlake T. and Bode J. (1994), Use of mutated FLP recognition target (FRT) sites for the exchange of expression cassettes at defined chromosomal loci. Bichemistry 33, 12746-12751.

Claim 56 is definite.

In view of the foregoing, Applicants respectfully Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has also been reconsidered and withdrawn is, thus, earnestly solicited.

Claims 17-25, 28-30, 32, 34-38, 43-46, 48 and 53-56 were rejected under 35 USC § 102(b) as being anticipated by Soriano, WO 99/53017. In response, Applicants remind the Examiner that anticipation requires that each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference, and, further, the absence in the prior art reference of even a single one of the claim elements is sufficient to negate anticipation. *In re Robertson,* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Soriano does not teach a functional DNA sequence comprising a selectable marker gene, as required by the present claims. Therefore, Soriano cannot anticipate the present claims.

Further on this point, Applicants emphasize that Soriano discloses the expression of DNA constructs in which the gene of interest is under control of an endogenous Rosa26 promoter. Moreover, Soriano discloses—in a separate embodiment—the integration of a marker gene under control of a heterologous PGK promoter (this construct is required for the selection of transgenic ES cells and does not represent a gene of interest according to the invention of the present invention). In the method of the invention of the present application, as exemplified, for instance, in the instant examples, a selectable marker is utilized for the identification of the integration event. Moreover, in the present method, the selection marker is part of the functional DNA sequence that also comprises the target gene under the control of a heterologous promoter. Novelty of the present claims is based on the fact that a heterologous promoter in the context of the Rosa26 locus is utilized for the expression of the target gene, which goes far beyond the selection of transgene ES clones according to Soriano and the functional DNA sequence further provides for the expression of a selectable marker gene. The method of the invention of the present application is thus novel over Soriano. Moreover, Applicant believes that the particular

construct of the invention of the present application which provides for the selection in addition to the expression of the target gene on the same construct is not rendered obvious by Soriano.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
NORRIS McLAUGHLIN & MARCUS, P.A.

By /Kurt G. Briscoe/
Kurt G. Briscoe
Attorney for Applicant(s)
Reg. No. 33,141
875 Third Avenue - 8th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844